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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/516,779	06/29/2005	Kevin L. Rozwadowski	4810-69922-01	5541

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ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/516,779	ROZWADOWSKI ET AL.	
	Examiner	Art Unit	
	Wu-Cheng Winston Shen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06/22/2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-13,16,17 and 20-28* is/are pending in the application.

4a) Of the above claim(s) *2* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,6-13,16,17 and 20-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 December 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application 10/516,779 is a 371 of PCT/CA03/00850 06/05/2003.

Applicant's After-Final amendments filed on 06/22/2007 has been received and entered. Claim 1 has been amended. Claims 5, 14, 15, 18, 19 have been canceled.

The Examiner withdraws the finality of previous office action mailed on 03/22/2007.

Applicant's reply filed on 06/22/2007 regarding traversal to the Restriction requirement has been considered. Claims 2, 6-13, 16, 17, 20, 21, and 24-28 are being newly considered because they have been amended to read on the elected invention, Group II, including claims1, 3, 4, 22 and 23, as indicated in the Restriction Requirement mailed on 12/01/2005, drawn to a method of modifying a target nucleic acid of interest at a target locus within a genome of a host; wherein the host is capable of expressing the RT at the same time as, or after, transforming the host, and a gene targeting construct. The restriction requirement is not being withdrawn, is held to be FINAL and groups are not being rejoined. The instant office action is being made Final because the newly considered and rejected claims are done so as a result of Applicant's amendments to the claims dated 12/04/2006 in response to the non-final action mailed on 06/02/2006.

The Examiner notes that amended claim 2 filed on 12/04/2006 remains in Group I, drawn to a method of modifying a target nucleic acid of interest at a target locus within a genome of a host, wherein the host is capable of expressing the RT prior to transforming the host, and a gene targeting construct, according to Restriction Requirement mailed on 12/01/2005.

Claim 2 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Status of claims: Claims 1, 3, 4, 6-13, 16, 17, and 20-28 are currently under examination.

Claim Rejection - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

1. Claims 6, 8, 9, 10, 11, 12, and 24-28 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is necessitated by claim amendments filed on 12/04/2006.

Claim 6 recites " The method of claim 1, wherein the gene targeting construct comprises *an msr coding region encoding an msr element* and *an msd coding region encoding an msd element*".

There are two issues render claim 6, and its dependent claims 8, 9, 10, 11, 12, and 24-28, unclear.

First, the specification does not disclose what msr and msd stand for. The phrases "msr" and "msd" are unclear because they are not specifically defined by the claim. Are they names of genes? Are they regulatory DNA sequences? Are they regulatory RNA sequences? Are they names of polypeptides? Or are they something else?

Second, based on the relevant disclosure in the specification, paragraph 0101, it appears that the phrases "*msr element*" and "*msd element*" are specific segment of DNA sequences because the sequences can be transcribed (See Fig. 1 of instant application). In this regard, it is

unclear what is means by the phrases "*an msr coding region encoding an msr element*" and "*an msd coding region encoding an msd element*". The Examiner notes that, in the context of gene expression, the phrase "coding region" commonly refers to the DNA sequences encode a polypeptide, not another DNA sequences whereas "x element" commonly refers to a *cis*-regulatory sequence, for instance TATA box recognized by TBP (TATA binding protein, a *trans*-regulatory factor).

Claim Rejection - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

2. The previous rejection of claims 1, 3, 4, 22, and 23 under 35 U.S.C. 102(e) as being unpatentable by Conrad et al. (Conrad et al. U.S. Patent Application Publication No: 2003/0082800 A1, Publication date, May 1, 2003), priority to 10/091998, hereafter referred to as Conrad et al.), is ***withdrawn*** because amendment of claim 1 filed on 06/22/2007.

Specifically, the phrase "wherein the message RNA is capable of self-primimg reverse transcription" in claim 1 has been amended to recite "wherein the message RNA self-primes

reverse transcription". Conrad et al. do not teach the message RNA self-primes reverse transcription.

Claim Rejection - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1, 3, 4, 7, 10, 13, 16, 17, 20, 21, 22, and 23 as amended are rejected under 35 U.S.C. 103(a) as being unpatentable over Conrad et al. (Conrad et al. U.S. Patent Application Publication No: 2003/0082800 A1, Publication date, May 1, 2003), priority to 10/091998) taken with Levin (Levin, A novel mechanism of self-primed reverse transcription defines a new family of retroelements. *Mol Cell Biol.* 15(6): 3310-7, 1995, cited previously). *This rejection is necessitated by amendment of claim 1.*

Conrad et al. provides guidance on an expression vector for altering expression of a target nucleic acid sequence in a host cell by production of single-stranded cDNA (ssDNA) in the host cell *in vivo*. The expression vector is comprised of a cassette comprising a sequence of interest, an inverted tandem repeat, and a primer binding site 3' to the inverted tandem repeat, and a reverse transcriptase coding gene, and may be transfected into the host cell in a method of sequence modification, such as site directed mutagenesis or gene therapy for therapeutic applications (See Abstract, paragraph [0018]). Transcription of the cassette by the host cell

produces an RNA template that is reverse transcribed with the product of the RT coding gene to produce ssDNA of a specified sequence. The resulting ssDNA binds to an endogenous target nucleic acid sequence (Abstract) wherein hosts that have a sequence modification at the target locus can be selected for (See paragraph [0093]). The cassette may be introduced into the host by transformation (See paragraphs [0022], [0045]). Wherein the ssDNA may contain any practical size sequence of interest as an insert, such as 31 bp, 1.2 kb, 2.4 kb in length (Fig. 4A, 4b, paragraphs [0099], 108-117). It is inherent that an insert used for site directed mutagenesis will have at least one bp that is different from the target nucleic acid sequence. Therefore in sequences less than 100 bp long this will provide for 99% or lower sequence similarity.

With regard to the limitation "the RT has a nuclear localization signal sequences" (NLS) (claims 7 and 10 of instant application), it is noted that the reverse transcriptase, taught by Conrad et al. and instant application, is synthesized in the cytoplasm and transported into nuclei to catalyze reverse transcription, and thereby the RT either been transported into nuclei by the presence of its own NLS or by association with other nuclear protein with NLS, which are encompassed by the limitation "the RT has nuclear localization signal sequences".

With regard to a selectable marker (claim 13 of instant application), Conrad et al. teach the specialized genetic elements include selectable marker genes so that the vector can be transformed and amplified in a prokaryotic system (See paragraph [0093], Conrad et al.).

With regard to a host cell (claims 16, 17, 20, and 21), Conrad et al. teach a prokaryotic or eukaryotic host (See, for instance, paragraph [0002], Conrad et al.). It is noted that the eukaryotic host taught by Conrad et al. reads on a yeast cell and a plant cell. Furthermore, a plant cell encompasses a yeast cell because yeast cells have cell wall and defined nuclear

membrane structures and are conventionally classified in mycology along with other multicellular fungi.

Conrad et al. does not teach that the message RNA self-primes reverse transcription and that yeast cells as host cells.

However, at the time of the filing of instant application, cDNA synthesis by reverse transcriptase via either a tRNA molecule binding to the 3' end of the mRNA or the 5' end of the mRNA bind to its own 3' end via a looping mechanism was known and evidenced in the art. For instance, Levin teach the inherent properties of render the Tf1 mRNA undergoing a self-priming mechanism of reverse transcription (See abstract, Fig. 1, page 3312, Levin, A novel mechanism of self-primed reverse transcription defines a new family of retroelements. *Mol Cell Biol.* 15(6): 3310-7, 1995).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to combine the method of the expression of ssDNA in vivo for altering gene expression in a host cell, by the teachings of Conrad et al., with the method for cDNA synthesis by reverse transcriptase via either a tRNA molecule binding to the 3' end of the mRNA or *the 5' end of the mRNA bind to its own 3' end via a mRNA self-primed looping mechanism*, by the teachings of Levin to achieve a method of modifying a target nucleic acid of interest at a target locus with a genome as recited in the claims of instant application.

One having ordinary skill in the art would have been motivated to combine the method of the expression of ssDNA *in vivo* for altering gene expression in a host cell, by the teachings of Conrad et al., with the method for cDNA synthesis by reverse transcriptase via either a tRNA molecule binding to the 3' end of the mRNA or *the 5' end of the mRNA bind to its own 3' end*

via a mRNA self-primed looping mechanism, by the teachings of Levin performed in yeast cells which are well established for genetic manipulation, to achieve a method of modifying a target nucleic acid of interest at a target locus with a genome as recited in the claims of instant application, because even in the presence of PBS (primer binding site) at 3' end of a mRNA, engineered 5' end sequences of a mRNA can alter the efficiency of self-priming efficiency and thereby affecting the efficiency of reverse transcription for synthesis of double stranded DNA, which in turn is required for homologous recombination mediated modification of a target nucleic acid of interest at a target locus within a host genome as recited in the claims of instant application.

There would have been a reasonable expectation of success given (1) the successful demonstration of the method of the expression of ssDNA *in vivo* for altering gene expression in a eukaryotic host cell, by the teachings of Conrad et al., and (2) the successful demonstration of the effect of 5'end sequences of Tf1 mRNA affect the mRNA self-primed looping mechanism for reverse transcription in yeast *S. pombe*.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Conclusion

4. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

5. No claim is allowed.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

THAIAN N. TON
PATENT EXAMINER

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